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Clinical Evaluation of Liver Structure and Function in Humans Exposed to Halogenated Hydrocarbons

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An unresolved question is whether humans exposed to comparatively low doses of persistent environmental chemicals such as polyhalogenated biphenyls or organochlorine pesticides are at risk for injury to the liver. Cross-sectional epidemiologic studies suggest that these chemicals may produce statistically significant but clinically mild abnormalities in the commonly employed chemical tests of liver function. The few reports of human liver morphology reveal nonspecific changes reflecting effects of lipophilic chemicals. There is evidence that chemicals of this category in at least some doses cause induction of liver microsomal enzymes involved in biotransformation of foreign substances. This finding has been documented by measurements of the clearance of model drugs or the appearance in the urine of steroid metabolites or glucaric acid. Although a positive statistical correlation between the concentrations of these chemicals in serum and the serum γ-glutamyltranspeptidase activity has been reported, the nonspecificity of the latter enzyme precludes conclusion that this change is indicative of induction of liver microsomal enzymes. Although the effects of this type of environmental chemical are not indicative of progressive liver disease, only prospective clinical trials can resolve the issue of the risk for future development of liver malignancy.

The liver plays a complex role in the interaction between man and his chemical environment. The liver serves as the major site for biotransformation and metabolic elimination of many foreign substances, but may also serve as a target organ for the toxicity of metabolically activated environmental agents. High doses of polychlorinated biphenyls (PCBs) or other lipophilic halogenated hydrocarbons in animals exert profound hepatoxic manifestations including liver cell necrosis, cholestasis, or in long-term exposure, malignancy. However, except for rare instances of overt poisoning of humans with these chemicals (*1*), the hepatic effects in man of exposure to halogenated hydrocarbons through environmental contact are generally inconspicuous (*2*).

Exposure to small amounts of PCBs and other chemicals in the environment produces subtle changes in standard clinical tests of liver function. Therefore most of the available information has, by necessity, come from cross-sectional epidemiologic studies examining primarily groups of people exposed to these chemicals because of their occupation. For example, several studies (*3–6*) of groups of electrical workers whose average serum or blood concentrations of PCBs were in the range of 33.4 to 524 ng/mL revealed statistically significant changes in liver tests, summarized in Table 1. However, the findings were not entirely uniform among these studies. A significant number of patients had liver enlargement on physical examination. The serum bilirubin tended to be in the lower range of normal whereas serum transaminase activity tended to be in the high normal range or slightly elevated. The serum γ-glutamyltranspeptase activity (γ-GTP) was positively correlated with the serum level of PCBs. The latter result was also reported in people exposed to sludge contaminated with PCBs (*7*) and in residents of Triana (*8*). The lack of consistency in demonstrating effects of PCBs on common liver tests is also reflected in new studies reported in this volume. There is one report that PCBs may cause induction of the liver microsomal drug-metabolizing enzyme systems in man (*9*) as is the case for experimental

Table 1. Effect of some environmental chemicals on clinical tests of the liver.[a]

		Liver test				
Agent	Hepatomegaly	BR	AST/ALT	γ-GTP	Enzyme induction	Reference
PCB	+	↓	↑	↑	+	(*4–9*)
Yusho	+	↑/↓	–	NR[a]	NR[a]	(*10–12*)
PBB	NR[a]	–	↑	↑	+	(*14,15*)
DDT	NR[a]	↓	–	↑	+	(*16–18*)
β-HCH	+	–	–	–	+	(*19*)
Chlordecone	+	–	–	–	+	(*20,21*)

[a]NR = not reported.

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animals. Yusho refers to the outbreak of poisonings in Japan in people who consumed rice oil that contained PCBs (*10*) plus polychlorinated dibenzofurans and dioxins. Initially, many of the patients presented with hepatomegaly and in one series 11% were said to show jaundice (*12*).

A more recent study, seven years after the outbreak, however, showed that there was a statistically significant reduction in serum bilirubin that correlated inversely with residual serum levels of poorly excreted PCB isomers (*13*). Transaminase levels were said to be normal. Studies of two large cohorts exposed to polybrominated biphenyls (PBBs) revealed no significant change in bilirubin, slight elevation in transaminase and in γ-GTP, and an elevation in urinary porphyrins that positively correlated with serum levels of the PBBs (*14,15*). Cross-sectional studies of groups with different serum DDT levels revealed hypobilirubinemia but no consistent relationship with transaminase (*16*). A positive correlation was found between the γ-GTP and the levels of serum DDT and its isomers in residents of Triana, AL (*17*). Evidence for induction of liver drug-metabolizing enzymes was found in one study of DDT workers (*18*).

β-Hexachlorocyclohexane (β-HCH, a component of lindane) is an insecticide ingredient that, like PCBs, is highly lipophilic and is slowly excreted from the body. In studies of workers occupationally exposed to HCH for up to 18 years there was still evidence of induction of liver enzymes 7 years after the last exposure. However, physical examination, the standard liver chemistry tests and rates of elimination of indocyanine green and galactose all were normal (*19*). Among the most complete data for an environmental agent of this class are the results of studies of 32 workers exposed to high concentrations of the insecticide chlordecone, known more commonly as Kepone. Despite the fact that these workers had high concentrations of chlordecone in their serum, adipose tissue, and liver (*20*), standard chemical tests were in each case repeatedly negative (*21*). However, there was liver enlargement and tests for liver microsomal enzyme induction were positive. Clearance of sulfobromophthalein (BSP) was normal in all of these patients. To summarize from the available data, one may conclude that the amounts of chlorinated hydrocarbons commonly found in humans are associated with changes in liver tests that are statistically significant and yet subtle and, thus, not readily recognized in the ordinary clinical setting.

Table 2. Liver histology in twelve patients with chlordecone poisoning.[a]

Finding	Number of patients
Light microscopy	
Vacuolated nuclei	3
Increased cytoplasmic (lipofuscin)	11
Fatty infiltration	3
Portal inflammatory cells (mild)	5
Portal fibrosis (mild)	3
Focal areas of proliferated reticuloendothelial cells	3
Electron microscopy	
Proliferated smooth endoplasmic reticulum	11
Dilated, vesiculated, rough endoplasmic reticulum	6
Lipid vacuoles	8
Branched mitochondria with paracrystalline inclusions	4
Blebs in hepatocyte sinusoidal membrane	4

[a]Reprinted by permission (*21*).

Despite the large numbers of people exposed to these chemicals there is surprisingly little information on human liver histopathology. The most complete information comes from 12 needle biopsy specimens from workers exposed to chlordecone (Table 2). Light microscopic examination revealed minimal steatosis, focal proliferation of reticuloendothelial cells and hypoglycogenation of nuclei. Two liver biopsies of patients exposed to PBBs (unknown levels) revealed only mild infiltration of both large and small fat droplets (*22*). Electron microscopic examination of liver specimens from patients exposed to chlordecone showed proliferation of the endoplasmic reticulum. There were also numerous residual bodies, branched mitochondria with paracrystalline inclusions, and blebs in the plasma membrane. The mitochondrial changes are nonspecific and have been noted in a wide variety of pathologic conditions of the liver. A report of one human liver biopsy in a patient exposed to PCBs also revealed proliferation of the smooth endoplasmic reticulum, increased numbers of residual bodies and nonspecific mitochondrial abnormalities (*23*). Perhaps the reason that there is so little human liver biopsy material available is that physicians believe liver biopsy is unwarranted in cases of exposure to PCBs or other related chemicals when liver tests are at most only minimally abnormal. This is unfortunate, because liver biopsy performed by an experienced hepatologist carries little risk and in the case of the chlordecone workers provided essential information for diagnosis and management and, ultimately, for designing a rational approach to treatment (*20,21*).

A prominent effect of lipophilic halogenated hydrocarbon chemicals both in animals and, apparently, in man is to induce the enzymes in the smooth endoplasmic reticulum responsible for xenobiotic biotransformation. This has generally been regarded as an adaptive response of the liver rather than as a manifestation of hepatotoxicity *per se*. However, induction of liver microsomal enzymes may alter the rate or pathways of metabolism of other xenobiotic or endogenous substrates. Many compounds that induce drug-metabolizing enzymes also are classified as tumor promotors in experimental carcinogenesis systems. Hence, it would be desirable to have simple, specific, and clinically practical tests that would recognize liver microsomal enzyme induction in man. One approach is measurement of the clearance of model drugs that rely on liver metabolism for their elimination. Clearance can be assessed from the rate of disappearance from plasma (for example, antipyrine or tolbutamide) or from the rate of appearance in the breath of metabolites derived from radio-

Table 3. Effect of lipophilic chlorinated hydrocarbons on clearance of antipyrine in humans.

Agent	Antipyrine half-life (*n*)		Reference
	Control	Exposed	
PCB	15.6 (5)	10.8 (5)	(*9*)
DDT (and others)	13.1 (33)	7.7 (26)	(*27*)
Lindane	12.9 (3)	11.7 (9)	(*28*)
β-HCH	14.7 (4)	7.4 (6)	(*19*)
Chlordecone	14.8 (3)	7.5 (10)	(*21*)

actively labeled drug substrates (for example, aminopyrine, caffeine or diazepam). Accelerated metabolism of these drugs in induced subjects is presumably due to accumulation in the microsomes of the cytochromes P-450, a group of hemoproteins capable of binding drugs and catalyzing the oxidative metabolism of many foreign and endogenous compounds. Indeed, urinary excretion of steroid metabolites may serve as a reflection of the cytochrome P-450-mediated drug-oxidizing activity since steroids also serve as substrates for these versatile hemoproteins. Many of the compounds that induce the cytochromes P-450 in the liver also induce microsomal enzymes involved in the metabolism of glucuronic acid (*26*). Therefore, increased urinary excretion of glucaric acid, a breakdown product of glucuronic acid, may signify proliferation of the smooth endoplasmic reticulum in the liver (*25*). It has been proposed that γ-GTP activity in the serum may also reflect microsomal enzyme induction in the liver (*26*).

It is surprising that the repetitively published generalities about the effects of PCBs and related chemicals on human liver microsomal enzymes have been derived from surprisingly few studies (Table 3). A significant reduction in the half-life of antipyrine disappearance from plasma was seen with groups exposed to PCBs (*9*), to a mixture of chlorinated hydrocarbons (primarily DDT but also including chlordane and lindane), to a skin cream containing lindane (*28*) and to β-HCH (*19*). Accelerated clearance of antipyrine from saliva was found in persons exposed to pesticides (*29*). Unfortunately, none of these studies compared the concentrations of the inducing agent in plasma or liver to the rate of drug metabolism so that the concentration these environmental agents required to achieve a threshold of induction in human liver is uncertain. However, it has been established that antipyrine half-life was shortened in chlordecone-poisoned workers (Table 3) at a time when the concentration of this pesticide in the plasma was no less than 1,000 ng/mL. Workers exposed to DDT exhibited urinary excretion of 6β-hydroxycorticosterol with a possible threshold for this effect being associated with a serum concentration of DDT of 300 to 500 ng/mL (*18*).

Excretion of urinary glucaric acid has received little attention as a way to test for microsomal enzyme induction in the liver by environmental chemicals. One study of workers exposed to DDT failed to reveal elevated excretion of urinary glucaric acid (*30*). However, the highest serum DDT concentration in this group (167 ng/mL) was less than the apparent threshold associated

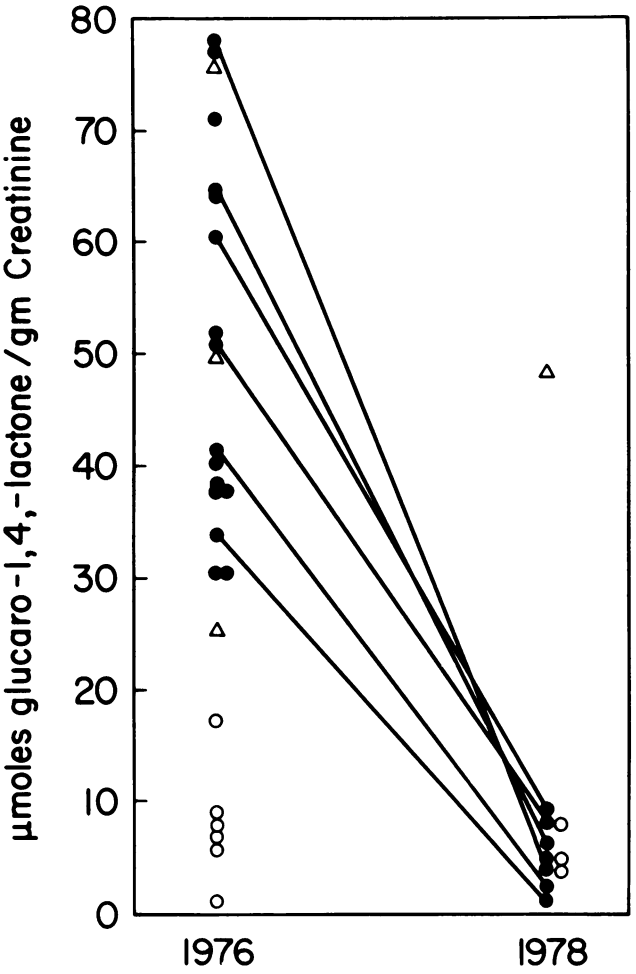

FIGURE 1. Urinary excretion of glucaric acid in workers exposed to chlordecone. At the time of initial evaluation (1976) and following cessation of cholestyramine therapy (1978), urine was obtained from workers exposed to chlordecone, and glucaric acid concentration was measured as described in the manuscript. The average values (μmole D-glucaro-1,4-lactone/g creatinine, mean ± SD) were (●) for the workers, 51.3 ± 16.5 in 1976 and 5.0 ± 2.4 in 1978; (○) for normal controls, 8.7 ± 5.3 in 1976 and 5.6 ± 2.2 in 1978; (Δ) for patients receiving drugs, 50.1 ± 25.0.

with liver enzyme induction in another group of DDT workers based on the measurements of drug clearance or excretion of steroid metabolites (*18*). Hence, it remains uncertain whether DDT (even in higher doses) affects urinary excretion of glucaric acid at all. Definitive evidence that an organochlorine chemical can increase urinary excretion of glucaric acid comes from studies of chlordecone-poisoned workers (*21*). As seen in Figure 1, urinary excretion of glucaric acid in workers was increased far above control values in the same range as three patients receiving inducing drugs for treatment of epilepsy. Moreover, after all the patients had been placed on cholestyramine, an orally administered anionic binding resin that stimulates the elimination of chlordecone from the body (*20*), the levels of chlordecone in the plasma fell to low or undetectable levels and the excretion of glucaric acid fell back into the normal range

in each case. From these results we have estimated that the serum level of chlordecone associated with enzyme induction in the liver is in the range of 100 to 500 ng/mL.

Epidemiologists have come to rely on the γ-GTP as a marker for induction of liver microsomal enzymes because the test is inexpensive and simple to perform. However, limitations in the significance of the γ-GTP must be fully appreciated. There is now extensive data regarding the localization of γ-GTP in human tissue. The enzyme is not found in the liver exclusively. Rather, γ-GTP is present in almost every tissue of the body (bone being a notable exception) with significant amounts in kidney, pancreas, spleen and intestine (*31*). A second important point is that γ-GTP is not a microsomal enzyme. In normal human liver (*32*) and in animal liver (*33,34*), γ-GTP has been localized to the hepatocyte plasma membrane. It is also found in the apical portions of some human bile duct cells (*32*). Unresolved is the question of whether small amounts of this enzyme are found also in nonparenchymal liver cells (*35*). Under some liver pathologic conditions in humans, γ-GTP activity is intensified in the area of the bile cannaliculus and this could account for increased activity in the serum. Even this point is uncertain, however, because despite elevated γ-GTP activity in the serum of patients with many types of liver disease, the overall activity of this enzyme in liver tissue was not necessarily increased (*36*).

Initial enthusiasm for the γ-GTP test may be subsiding because of the realization that γ-GTP (*36*) activity in human serum is increased in association with so many physiologic conditions. It is true that patients receiving some drugs, particularly antiepileptic drugs such as barbituates and phenytoin, have significantly increased γ-GTP activity (*26,27*). However, the enzyme is increased in almost every form of hepatobiliary disease (*36,38–41*) and because the test is among the most sensitive, it will be elevated in subtle forms of liver injury such as resolution of asymptomatic viral hepatitis (*42*). γ-GTP is also elevated in diabetes or other pancreatic diseases (*31,43*), in kidney diseases (*44*) and, for reasons that are unclear, with congestive heart failure (*45*), angina (*46*) myocardial infarction (*47*) and many other conditions (*48*), even though there may be no apparent effect of these diseases on the liver. A most troublesome confounding factor that may complicate the usefulness of γ-GTP in epidemiologic studies is that consumption of alcohol even in moderate amounts may elevate the γ-GTP activity in as many as 70% of the subjects (*49–54*). Another confounding factor is that the test is elevated in babies and also appears to be higher in adult males than in females (*55*). Indeed, birth control pills appear to decrease γ-GTP at least under conditions where the enzyme is elevated in viral hepatitis (*56*).

In addition to "false positive" results for liver enzyme induction the γ-GTP can give "false negative" results as well. For example, administration of rifampicin to normal subjects increased clearance of hexobarbital and urinary glucaric acid, and yet γ-GTP activity remained normal (*57*). In at least one patient given dichlor phenazone, warfarin clearance was accelerated whereas γ-GTP activity remained unchanged (*26*), although dichlorophenazone did increase γ-GTP in most subjects (*26*). Finally, despite the strong evidence for induction of liver microsomal enzymes in chlordecone-poisoned workers, γ-GTP activity remained normal (*21*). Thus an elevated γ-GTP activity, particularly as taken out of clinical context in an epidemiologic study, need not indicate liver involvement, whatsoever, let alone induction of drug-metabolizing enzymes in the liver. Hence, while reported associations between γ-GTP activity serum levels of PCBs or of DDT stand as valid statistical associations conclusions that the elevation of γ-GTP activity represents liver microsomal enzyme induction must be regarded as tentative pending further substantiation.

In summary, environmental agents produce subtle yet statistically demonstrable changes in human liver at least as judged by routine chemistry evaluation. Unfor tunately, insufficient data is available relating liver concentrations of these chlorinated compounds and detectable changes in liver tests to be able to establish with confidence threshold levels for observable effects. There is no evidence that these subtle changes are likely to lead to clinically significant liver disease. However, because these chemicals produce liver malignancies in experimental animals there will continue to be concern about human liver cancer until appropriate epidemiologic studies are carried out.

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